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REVIEW ARTICLE

The role of T cells in psoriasis

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ABSTRACT

Evidence for a key role of T cells in the pathogenesis of psoriasis has come from both experimental and clinical data. Initially, generalized immunosuppressants, intended for use in transplant settings, were found to improve clinical signs and symptoms of psoriasis. Their efficacy attracted attention to the activated T cells that are a major component of the inflammatory infiltrate of psoriatic lesions. Further research determined that T cells from patients with psoriasis could transmit disease in animal models. These findings laid the groundwork for characterizing the pathogenesis of psoriasis as immune mediated with skin-directed T cells playing a central role. Once these pathogenic T cells have entered the skin, they become activated and release cytokines and chemokines to attract other immune cells to perpetuate the inflammatory cascade. As the role of the T cell in psoriasis has evolved and understanding of immunopathology has increased, a multitude of biologic targets have been revealed. Newer strategies for the treatment of psoriasis have therefore focused on modifying T cells in this disease through direct elimination of activated T cells, inhibition of T-cell activation, or inhibition of cytokine secretion or activity. The mechanisms by which these new biologic agents act on psoriasis will affect their profile of efficacy and safety. Important selection criteria for optimal antipsoriatic therapies include long-term safety and tolerability, ability to produce long-lasting remissions, and convenient dosing regimens.

Key words: biologic therapy, cytokine, immunopathogenesis, psoriasis, T cell

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Introduction

Psoriasis is a chronic inflammatory skin disorder afflicting up to 2.5% of the world's population.[1,2] The disease is characterized by epidermal hyperproliferation and inflammation, which lead to the clinical feature of bright red, elevated, scaly plaques.[3,4] Presently, a large and growing body of clinical and experimental evidence supports a key role for T cells in the pathogenesis of psoriasis.[4–8]

The observation that cyclosporin, a generalized T-cell immunosuppressant, could dramatically alleviate severe psoriasis symptoms suggested that T cells were involved in the disease process.[9–12] Reports that bone marrow allografts could either clear or transfer psoriasis reinforced the idea that the disease might have a primary immune basis.[13,14] More recently, in experiments with immunodeficient mice receiving engrafted healthy skin from patients with psoriasis, the injection of autologous blood-derived T cells from these patients successfully transmitted the disease.[15]

The inflammatory infiltrate in psoriatic lesions is dominated by an influx of $CD4^+$ and $CD8^+$ T cells bearing cell-surface markers of activation (CD25 [interleukin-2 receptor], CD27, CD69) and memory (CD45RO).[16–18] Lesional T cells also express the skin-homing receptor, cutaneous lymphocyte-associated antigen (CLA).[19] Importantly, infiltration of these T cells is one of the earliest events in the evolution of psoriatic plaques.[20,21] The clinical manifestations of psoriasis follow T-cell infiltration as the activated memory (or memory-effector) T cells generate cytokines such as interleukin (IL)-2, tumour necrosis factor-α (TNFα) and interferon-γ (IFNγ), which stimulate recruitment of more inflammatory cells and the epidermal changes characteristic of psoriasis.[17,22–27]

These data provide compelling evidence of aberrant T-cell involvement in producing the symptoms of chronic plaque psoriasis. Advances in psoriasis treatments are based on this key role of T cells in disease pathogenesis. This review will first describe the general principles of T-cell immunopathology in

psoriasis that provide the rationale underlying the mechanisms of action of these new immunotherapies, and then will give a review of clinical data.

T-cell immunopathology in psoriasis

Normal immune surveillance in the skin (fig. 1)

T cells are key surveillance elements of the immune system that proliferate during a first encounter with an infectious agent or other foreign antigen.[28] In the skin, antigens are internalized by dendritic or Langerhans cells where they are processed and presented on the cell surface. These antigen-presenting cells (APCs) transit to the lymph node and initiate a complex activation process by interacting with naïve T cells, which have not encountered an antigen previously. This primary (acquired) immune response generates both T cells and antibody-secreting B cells as well as specialized memory T and B cells with highly specific cell surface receptors for the antigen.[29]

The status of cell maturation and activation is indicated by specific molecules expressed on the cell surface. Memory-effector T cells express the low molecular weight isoform of the tyrosine phosphatase CD45 ($CD45RO^+$), and naïve T cells express the high molecular weight isoform of CD45 ($CD45RA^+$). Memory markers also include the site of first antigen contact. In lymph nodes that drain the skin, memory T cells acquire the skin-homing receptor CLA, which programs them to selectively migrate to the skin and thus recall where the antigen was first encountered.[4] Based on findings from biopsies of psoriatic lesions, these memory skin-homing T cells are substantial components of the inflammatory infiltrate.[16–19]

A normal immune response continues with the release of proinflammatory (or type I [Th1]) cytokines, including IL-1, TNFα and IFNγ.[8] These cytokines activate transcription factor nuclear factor κB (NFκB), which further perpetuates an immune-mediated inflammatory cascade.[30] Expression of intercellular and vascular adhesion molecules (ICAM and VCAM, respectively) recruits additional inflammatory cells.

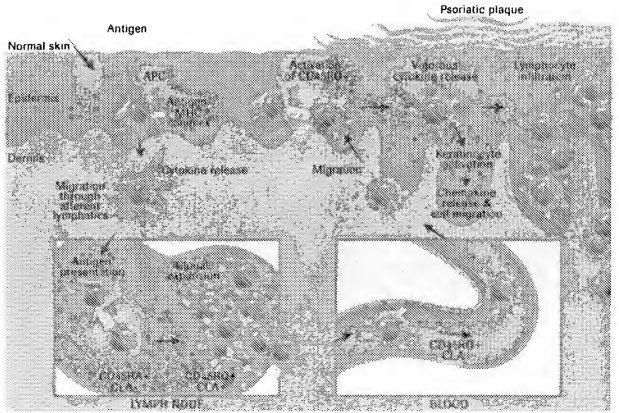

fig. 1 Generation of a T-cell response in the skin. This figure presents the sequence of cellular immune activation and trafficking pathways of APCs and T cells. The response begins with antigen capture by APCs (Langerhans cells in the epidermis). These cells mature and migrate to lymph nodes, where molecular interactions between APCs and a naïve T cell ($CD45RA^+$) lead to activation of the T cell, during which the lymphocyte acquires the skin-homing receptor CLA and differentiates into memory cells ($CD45RO^+$) that are type 1 or type 2 effectors. These $CLA^+CD45RO^+$ memory T cells enter the circulation and exit cutaneous blood vessels at sites of inflammation. In the dermis or epidermis upon encountering the antigen, the T cells become activated and release cytokines or exert other effector functions. In the normal immune response, antigens are eliminated by T-cell-stimulated pathways in the skin and then the immune response ends. In psoriasis, T-cell infiltration and effector responses persist chronically. MHC, Major histocompatibility complex.

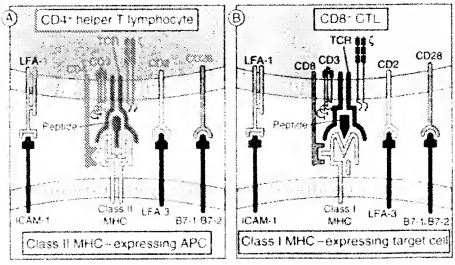

fig. 2 Activation of T cells. The interaction of a $CD4^+$ (A) and a $CD8^+$ (B) T cell with an APC or target cell involves multiple T-cell membrane proteins that recognize different ligands. Not all accessory molecules are shown. LFA, leucocyte function-associated antigen; MHC, major histocompatibility complex; TCR, T-cell receptor. Reprinted with permission from Abbas *et al.* (ref. 28).

In psoriasis patients, this 'normal' immune response is excessive in the skin.[4] The presence of an increased number of circulating skin-directed memory T cells in patients with psoriasis can lead to initiation of the inflammatory cascade as just described in response to even minor trauma. It is unclear if the pathologic events that drive the development of psoriasis lesions are the result of a unique repertoire of cytokines or whether skin cells of psoriasis patients are hypersensitive to inflammatory cytokines. Psoriasis has been associated with several gene regions critically involved in immune-mediated responses.[3,6,25,31,32] Whether psoriasis is an autoimmune disease continues to be debated. Initially, researchers had proposed a role for superantigens as disease triggers.[8,33–35] Yet, analysis of the lesional psoriatic T-cell receptor (TCR) usage clearly provided evidence of an antigen-driven T-cell activation.[36,37] The continuous presence of the same clonal TCR rearrangements within psoriatic skin lesions and the identification of conserved psoriatic TCR rearrangements indicated that the same antigens and effector T cells are involved in psoriatic inflammation over prolonged periods of time.[38–40] Furthermore, they suggested that there is a common psoriatic antigen in different patients. This finding is in accordance with psoriasis being an autoimmune disorder. The precise antigenic trigger for psoriasis, however, remains unknown.

Irrespective of the elusive nature of the psoriatic trigger, the identification and understanding of these processes have provided targets for the development of biologic therapies directed against the pathogenic T cells. The common goal of new therapeutics is to reduce or eliminate the pathogenic effects of the aberrant T cells. Thus, the new biologic agents have been designed to target various aspects of T-cell activation and secretion of cytokines. Numerous agents have been developed and their targeted mechanisms of action have serendipitously led to other effects.

T-cell activation

T-cell activation is a complex sequential process requiring interaction with APCs and involving at least two signals for complete activation and proliferation (fig. 2).[4–29] The primary signal originates when dendritic cells recognize, capture, internalize and process exogenous antigen or its peptide fragments[41] for presentation to the T cell via a complex of antigen-presenting proteins.[42,43] These protein complexes on the surface of the APC critically involve the human leucocyte antigen (HLA) major histocompatibility complex (MHC) molecules. Class I and class II MHC molecules present the peptide antigen to TCR on $CD8^+$ or $CD4^+$ T cells, respectively (fig. 2).[4,29,44] The TCR varies with different specificities of T cells and is composed of α/β or γ/δ heterodimer chains. Each chain contains an antigen-specific variable region and an invariant domain, which is associated with a CD3 complex on the T-cell surface that transmits activation signals into the cell when the TCR binds antigen-MHC.[29,44] Both $CD4^+$ and $CD8^+$ T cells influence signal transduction through the TCR during immune recognition.[45] $CD4^+$ cells typically act as 'helper' cells, recognizing antigens bound to MHC class II molecules on the APC. $CD8^+$ cells are usually cytotoxic T lymphocytes, containing the proteins granzyme[46] and perforin[47] (for inducing apoptosis of the target cell), and they recognize antigen presented by MHC class I molecules. When cross-linking of the TCR with MHC complexes initiates an activation signal, a downstream transcriptional cascade begins to mediate proliferation and cytokine production.[44]

The second, or 'costimulatory', signal for activation is transduced by a number of cell surface interactions between the T cell and the APC that involve discrete pairs of molecular markers.[48–51] Some of these costimulatory receptor-ligand pairs also have cell adhesive functions, and are essential for optimal initiation and maintenance of T-cell proliferation and cytokine production. Simultaneous delivery of both signals is crucial for initial activation of T cells; cells exposed to signal 1 in the absence of signal 2 cannot become fully activated and may become functionally unresponsive or anergic.[52]

Three of these costimulatory pathways are of major importance in inducing specific immune response profiles in memory T cells: CD2/leucocyte function-associated antigen (LFA)-3, LFA-1/ICAM-1 and CD28/B7.[51] A fourth costimulatory pathway involving CD40/CD40 ligand has been defined recently.[53] These pathways are especially crucial in the development of new therapies for psoriasis, because blocking the interaction between one or more of these receptor-ligand pairs can prevent the primary T-cell activation response, irrespective of the inciting antigen.

Shortly after antigen stimulation, naïve T cells increase expression of CD2 and LFA-1 to facilitate costimulatory interactions with APCs.[51,54] Increased expression of these molecules persists after reversion to a resting state and thus serves as a hallmark for the memory cell phenotype.

T-cell trafficking from blood to skin: activation markers and adhesion factors

Once activated, the naïve T cells undergo the transition to memory T cells and acquire the specific combinations of adhesion molecules and receptors needed to transit out of the lymph nodes and enter extranodal tissues from the circulation (fig. 3).[55–57] The expression of CLA and of the chemokine receptor CCR10 are quite unique to memory T cells involved in inflammatory skin diseases. Not only do CLA and CCR10 identify skin-specific T cells, they also mediate tethering of T cells to the endothelium in cutaneous venules and direct T-cell migration to the dermal extracellular matrix and basal keratinocytes.[19,58,59]

Accumulation of activated memory T cells into psoriatic skin is initiated by a series of interactions of several glycoprotein ligands and chemokine receptors on the T-cell surface (CLA, ICAM-1, CCR10) with a variety of adhesion factors on vascular endothelium (P-selectin, E-selectin, CCL27).[4,59,60] P-selectin and E-selectin are upregulated on endothelial cells during cutaneous inflammation and bind to T cells through P-selectin glycoprotein ligand-1 (PSGL-1).[60,61] CLA is an inducible carbohydrate modification of PSGL-1. In fact, both lesional and nonlesional skin of psoriatic patients shows an increased overall expression of several of these adhesion receptors. For example, E-selectin is increased on endothelial cells and ICAM-1 has been shown to be upregulated on T cells.[62] Furthermore, in psoriasis and other inflammatory disorders, CCL27 is highly upregulated by basal keratinocytes and secreted into the papillary dermis where it is immobilized on the extracellular matrix and on the surface of endothelial cells.[59] Binding of CCR10 to the skin-associated chemokine CCL27 is considered essential for the migration of T cells into lesional skin, and neutralization of CCL27 in a mouse model of skin inflammation impairs lymphocyte recruitment.

The selectins form temporary bonds (tethering) with oligosaccharide receptors on the T-cell surface despite shear pressure from rapid blood flow. Shear pressure causes bonds upstream to dissociate, while new bonds form downstream, producing a slow rolling motion of the T cell. This motion exposes the T cells to chemokines produced by resident skin cells and displayed on the endothelial surface. These chemokines (e.g. monocyte chemotactic protein [MCP]-1, 3 and 4; macrophage inflammatory protein [MIP]-1α and -β; inducible protein [IP]-10; regulated on activation, normal T-cell expressed and secreted [RANTES]) can be up- or downregulated to assist proper routing of the T cells.[60]

To complete its extravasation into the skin, the T cell must stop rolling by engaging additional secondary receptors belonging to the integrin family, including LFA-1 (CD11a-CD18) and very late antigen (VLA)-4.[60,63,64] These integrin receptors form high-affinity bonds, arresting the rolling process of the CLA+ T cell, and favouring its flattening in preparation for extravasation through the endothelium.[4] On the abluminal side of the vessel, the T cell responds to chemotactic signals from the site of injury or infection. Enhanced expression of adhesion receptors on psoriatic skin facilitates increased influx of activated T cells.[4]

T cells and cytokines

The principal clinical features of psoriasis – inflammatory infiltrate and epidermal hyperproliferation with abnormal keratinocyte differentiation – appear to be driven mainly by various cytokines and chemokines released by the activated, skin-homing pathogenic T-cell population.[4,65] Once activated, T cells secrete a wide variety of cytokines capable of stimulating neighbouring cells (e.g. dendritic cells, macrophages, keratinocytes), which in turn secrete additional cytokines, generating a positive feedback cycle that maintains the chronic inflammatory state.[65]

Functional analysis of T cells isolated and cloned from psoriatic skin lesions showed that they could evoke epidermal keratinocyte proliferation by secreting a variety of mediators.[23,24,26] Although there remains some debate,[27,65] several investigators have suggested that a proinflammatory or Th1 cytokine profile (i.e. IL-1, IL-2, IFNγ) predominates in the psoriatic T-cell response (Table 1).[27,66,67] This cytokine pattern is typically associated with T-cell responses to autoimmune tissue injury.[68] Although activated CD4+ T cells are the primary source of

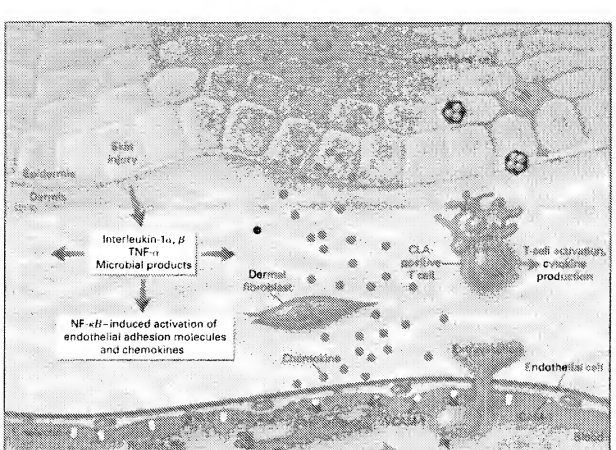

fig. 3 Trafficking of a CLA+CD45RO+ T cell into inflamed skin. Cytokine receptors (including IL-1 and TNFα) activate NFκB to transcript many genes that contain κB sites. In endothelial cells, these include the adhesion molecules E-selectin, ICAM-1 and VCAM-1. The process of extravasation to the skin begins with the T cells slowing in velocity within the circulation. The T cells use CLA-P-selectin glycoprotein ligand 1 (CLA-PSGL-1) cell-surface molecules to bind to E-selectin and P-selectin on the luminal surface of the cutaneous postcapillary venules, a process called 'tethering'. The T cells then roll on the endothelial surface in the direction of blood flow. Chemokines are transported to the endothelial cells and binding of these chemokines to specific T-cell receptors results in a modification of the structure of the lymphocyte-function-associated antigen 1 (LFA-1) and the very late antigen 4 (VLA-4) so they can bind to ICAM-1 and VCAM-1, respectively. This binding results in flattening of the lymphocytes in preparation for their extravasation. Reprinted with permission from Robert and Kupper (ref. 4).

Table 1 Principal cytokines involved in pathogenic steps leading to clinical expression of psoriasis[45]

Cytokines	Endothelial activation	Immunocyte recruitment	Keratinocyte–immunocyte interactions	Amplification of inflammatory mechanisms	Keratinocyte hyperproliferation
IL-1	√	√	√	√	√
IL-2				√	
IL-6	√			√	√
IL-8	√	√	√	√	√
TNFα	√	√	√	√	
IFNγ	√		√	√	√
MCP-1		√		√	
GM-CSF					√

IL, interleukin; TNFα, tumour necrosis factor α; IFNγ, interferon γ; MCP-1, monocyte chemoattractant protein-1; GM-CSF, granulocyte-macrophage colony-stimulating factor. Due to pleiotropism and the induction activity of each cytokine on the others, a strict, definite classification cannot be presented.

cytokines,[14] other cells within and outside of the immune system also produce these cytokines. $CD8^+$ cytotoxic killer cells, for example, produce IFNγ and TNFα, and contribute to Th1-like responses.[69] IFNγ may act cooperatively with other growth factors to enhance keratinocyte proliferation.[26] A newly discovered cytokine, IL-20, has recently been suggested as another factor regulating keratinocyte participation in inflammation.[70]

Whether the T cells causing psoriasis belong principally to the $CD4^+$ or $CD8^+$ T-cell subset is uncertain.[38,71–73] A major contribution of $CD4^+$ T cells to initiation and maintainance of psoriatic inflammation has been suggested by the efficacy of systemic treatment with monoclonal CD4 antibodies, even in severe cases of psoriasis.[74–76] Immunodeficient mice bearing xenografts of normal areas of human skin from psoriatic patients developed psoriasis after intradermal injection with autologous $CD4^+$ T cells.[71] However, psoriasis can worsen in patients with active human immunodeficiency virus (HIV)-acquired immunodeficiency syndrome (AIDS) despite a falling $CD4^+$ cell count.[77] Both $CD4^+$- and $CD8^+$-activated T cells have been found in psoriatic plaques.[16,73] It now appears that a functional interaction between both T-cell subsets in psoriasis seems most likely, with $CD8^+$ T cells depending on $CD4^+$ T-cell help to create an appropriate environment to permit activation and clonal expansion of additional dormant epidermal $CD8^+$ cells.[38,72]

NFκB is involved in induction of inflammatory cytokines and chemokines in keratinocytes and fibroblasts.[4,30,51] NF-κB-mediated gene transcription initiates postreceptor signal transduction events that result in transcription of cytokine and cytokine receptor genes and also can induce expression of E-selectin, ICAM-1 and VCAM-1 in cutaneous endothelial cells.[4] Translocation of NFκB can also be initiated by ultraviolet irradiation, cytokines, certain viruses, mitogens and oxidants.[30]

Therapeutic mechanisms for targeting T cells in psoriasis

The immunologic cascade described above establishes the necessary activities of the T cell that are responsible for induction and propagation of disease activity. These immunologic activities and responses can be modified by biologic therapies. The specific targets for biologic agents developed and tested in psoriasis are described below in conjunction with clinical data on the individual therapies.

Elimination of activated T cells

Removal of the activated pathogenic T-cell population would be expected to ameliorate the disease process. As described previously, T cells involved in the pathogenesis of psoriasis are defined by several cell-surface receptors and markers. The pathogenic T cells come from a pool of cells that express activation and memory markers, such as the high-affinity IL-2 receptor and $CD45RO^+$, and they are CLA^+. CD2 and LFA-1 expression is higher on activated memory T cells compared with naïve T cells, suggesting that they may be specific targets for activated T cells.[16,54,78]

Removing the source of the pathogenic T cells offers the potential for a prolonged duration of response following cessation of treatment. Therapies with this attribute are considered remittive. Currently, PUVA therapy is the only remittive therapy for psoriasis, producing long remissions after therapy is complete.[79] This differential effect has been associated with the ability of PUVA treatment to nearly ablate tissue-infiltrating lymphocytes in psoriatic skin.[80,81] Importantly, however, the mechanism by which T cells are reduced must be selective, because generalized T-cell reduction would likely be associated with a substantial risk of infection or other immunotoxicities.

One of the first biologic agents found effective against psoriasis was a direct T-cell toxin.[82] Denileukin diftitox (DAB_{389}IL-2; Ontak®, Ligand Pharmaceuticals, San Diego, CA, USA) combines the binding site of IL-2 with a subunit of diphtheria toxin, binds to T cells directly, becomes internalized and releases the toxin to destroy the pathogenic T cell.[83] Two small studies in patients with psoriasis showed evidence of clinical benefit, however, in the second study, three times weekly doses of 5, 10 or 15 μg/kg IV for 4 weeks were poorly tolerated in these patients, producing serious adverse events at the highest doses.[84] A third dose-ranging study using lower doses (0.5, 1.5 or 5 μg/kg IV) recently reported ≥ 50% improvement in PASI scores for seven of 15 patients with severe psoriasis who received 5 μg/kg IV given daily for three consecutive days every other week for 8 weeks.[85] Though better tolerated in this study compared with the earlier trials, DAB_{389}IL-2 treatment not only produced dose-related antibodies (to IL-2 and to the agent itself), but several patients experienced moderate-to-severe adverse events (e.g. transaminase elevation, leukopenia, exfoliative dermatitis) that will require careful monitoring over acute and long-term treatment in future trials.[85]

Two other biologic agents have been found to reduce the number of circulating activated T cells and provide improvement in psoriasis. Alefacept (LFA-3/IgG_1; Amevive®, Biogen, Cambridge, MA, USA) is a novel and selective biologic agent composed of the first extracellular domain of LFA-3 fused to the hinge, C_H2 and C_H3 sequences of IgG_1. Each component of alefacept binds to unique targets and, together, contribute to its mechanism of action.[86–89] The LFA-3 portion binds to CD2 on T cells and blocks the interaction of LFA-3 on APCs, inhibiting T-cell activation and proliferation. The Fc portion binds to FR_γRIII receptors on accessory cells (e.g. natural killer cells and macrophages) and induces selective T-cell apoptosis. Because CD2 is upregulated on memory T cells,[54,78] the actions of alefacept result in reductions in $CD4^+$ and $CD8^+$ memory T-cell subsets.[90,91] Naïve T cells, B cells and natural killer (NK) cells remain relatively unchanged during alefacept treatment.

Results of a phase II, multicentre, multidose, placebo-controlled trial ($n = 229$) showed that alefacept improved psoriasis and was well tolerated.[91] Patients were randomized to one of three alefacept doses (0.025, 0.075 or 0.150 mg/kg) administered by 30-s IV bolus or placebo for 12 weeks. At 2 and 12 weeks after treatment, the percentages of patients achieving ≥ 50% and ≥ 75% PASI reduction from baseline were significantly higher in the alefacept groups than in the placebo group. At 12 weeks after treatment, 47%, 63% and 42% of patients in the alefacept 0.025, 0.075 and 0.150 mg/kg groups, respectively, had ≥ 50% PASI reduction from baseline compared with 32% of patients in the placebo group ($P = 0.02$). For ≥ 75% PASI reduction, 33%, 31% and 19% of patients in the three alefacept groups, respectively, achieved the endpoint compared with 11% of placebo patients ($P = 0.02$).[91] Clinical improvement was related to reduction in memory T cells.[91] As expected from its mechanism of action, clinical responses were durable. Patients who had a PGA of 'clear' or 'almost clear' did not require further systemic treatment for psoriasis for a median of 10 months (range, 6–18 months).[91] Furthermore, there were no reports of disease rebound or flare after treatment was stopped.

Alefacept was well tolerated in the phase II trial, with no reports of systemic toxicities or serious drug-related adverse events.[91] Importantly, reductions in T-cell counts have not been associated with an increased risk of infection or malignancy.[91] To further evaluate the ability of patients receiving alefacept to respond to infectious organisms or other foreign antigens, immune responses to a novel and recall antigen were compared in psoriatic patients receiving alefacept or control.[92] Responses to both antigens were comparable between alefacept and control groups and similar to normal volunteers. Alefacept did not blunt normal immune responses to novel or recall antigens.

Pivotal double-blind, placebo-controlled, multicentre phase III studies of the efficacy and safety of alefacept in over 1000 patients with chronic plaque psoriasis have also been completed, with results reported recently.[93,94] In one study, patients received two 12-week courses of alefacept 7.5 mg or placebo given once weekly by IV bolus injection, with each course separated by at least 12 weeks of follow-up. Patients were randomized into three equal cohorts: alefacept followed by a second course of alefacept, alefacept followed by placebo, or placebo followed by alefacept.[93] In the second phase III study, patients were randomized to alefacept 10 mg, 15 mg or placebo by intramuscular injection once weekly for 12 weeks, with 12 weeks of treatment-free follow-up.[94] In both the IV and IM studies, significantly more patients treated with alefacept achieved the primary endpoint, a 75% or greater reduction in PASI, than patients receiving placebo. In patients receiving two IV courses of alefacept, 71% and 40% achieved a 50% or greater and a 75% or greater reduction in PASI, respectively. Clinical improvement in responders was durable, with a median duration of response of 7 months in the IV study. In both studies, alefacept conferred significant ($P < 0.001$) quality of life benefits, as assessed by the Dermatology Life Quality Index (DLQI). The safety profile was consistent with earlier phase I and II studies. (These data were presented at the American Academy of Dermatology annual meeting, New Orleans, LA, February 2002.)

Siplizumab (MEDI-507, MedImmune), a humanized anti-CD2 monoclonal antibody, binds CD2 and selectively eliminates activated T cells and NK cells.[95] Three phase I/II studies of siplizumab by IV or subcutaneous (SC) injection in patients with moderate to severe psoriasis have been conducted.[96] In all studies, siplizumab was found to be generally safe and well tolerated.[96] Reductions in PASI scores were observed, however, the most effective dose has yet to be determined. For patients receiving either 40 μg/kg/week for 8 weeks in the IV study or 5 or 7 mg/week for 12 weeks in the SC study, more than 55% experienced at least a 50% PASI reduction and more than 33% had at least a 75% PASI reduction.[97] Further studies have been initiated to evaluate the utility of siplizumab for psoriasis.[96]

Inhibition of T-cell activation

Identification of the costimulatory pathways involved in T-cell activation (fig. 2) has provided several targets for biologic agents. Pharmaceutical researchers have responded with agents directed against each of these identified targets. By inhibiting the T-cell activation process, the immune response that drives psoriasis pathogenesis is reduced. However, since the potential also exists to interfere with normal immune responses to foreign antigens, such as infectious agents, clinical studies are essential to verify maintenance of normal immune function during treatment.

As mentioned previously, alefacept targets the CD2/LFA-3 pathway; however, pharmacodynamic data indicated a dual mechanism of action, with selective reduction of memory T cells as the primary effect. The LFA-1/ICAM-1 pathway is inhibited by efalizumab (anti-CD11a; Xanelim™, Genentech, San Francisco, CA, USA), a humanized monoclonal antibody that targets the CD11a component (α subunit) of LFA-1. Because increased expression of ICAM-1 facilitates extravasation of T cells into lesional skin, efalizumab also may block T-cell trafficking into the skin.[98] In a double-blind, placebo-controlled, phase II trial, 145 patients with moderate to severe psoriasis were sequentially enrolled to receive efalizumab at a low dose (0.1 mg/kg, $n = 22$) or high dose (0.3 mg/kg, $n = 75$) or placebo ($n = 48$). Treatments were administered weekly by 90-min IV infusion for 8 weeks. A significantly higher percentage of patients receiving high-dose efalizumab had improvement in physician global assessment (PGA) than did those receiving placebo 1 week after the last dose. No significant differences between patients receiving low-dose efalizumab and placebo were observed. PGA ratings of at least excellent occurred in 25% of patients receiving high-dose efalizumab compared with 2% receiving placebo ($P = 0.0003$).[98]

Efalizumab was well tolerated, with no increased risk of infection or malignancy observed. Psoriasis was reported in the

phase II trial as an adverse event more frequently in the high-dose efalizumab group compared with placebo. A positive antibody response to efalizumab was found in 14% of patients in the high-dose group. In another study, humoral immune responses to a novel antigen were suppressed in patients receiving a single dose of efalizumab.[76] The effects of these findings on long-term use warrant further study.

Two randomized, placebo-controlled phase III studies have evaluated the efficacy, safety and tolerability of efalizumab in more than 1000 patients. Preliminary results have been released by Genentech[99] and were presented at the American Academy of Dermatology (2002). The design of the two trials was similar; patients were randomized to treatment with an initial conditioning dose of 0.7 mg/kg in the first week, followed by either 1 mg/kg or 2 mg/kg of efalizumab or placebo SC for 12 weeks. The percentage of patients who achieved a 75% or greater reduction in PASI was significantly higher in the efalizumab groups compared with the placebo group for the pooled results of the two studies (29% for 1 mg/kg, 28% for 2 mg/kg and 3% for placebo), with no difference between the two doses of efalizumab. Secondary measures of efficacy, including PGA of 'excellent' or 'clear', overall lesion score of 'minimal to clear', plaque thickness and quality of life were markedly improved with efalizumab therapy. Long-term safety and efficacy results of efalizumab maintenance therapy from these 1-year studies are pending.

The CD28-B7 costimulatory pathway is a target for several compounds. The CD28 (CTLA4) receptor on T cells binds to the B7 molecule on the surface of APCs and stimulates T-cell proliferation. The fusion protein, CTLA4Ig, binds to B7-1 (CD80) and B7-2 (CD86) expressed on APCs.[100,101] Despite early findings of clinical activity against psoriasis, CTLA4Ig diminished patients' ability to mount T-cell dependent antibody responses to immunogens.[101] Further development of CTLA4Ig is focused on rheumatoid arthritis and organ transplantation.

Anti-CD80 (IDEC-114, IDEC Pharmaceuticals Corporation, San Diego, CA, USA) is a primatized monoclonal antibody that binds to B7.1 (CD80), blocks the interaction of CD28 with CD80 and inhibits T-cell activation.[102] In a phase I/II trial of 35 patients with psoriasis, a ≥ 50% PASI reduction from baseline at some time during the study was observed in 40%.[103] Maximum effects on PASI were observed 12 weeks after the last dose. Adverse events included mild uncomplicated colds, transient chills and mild fatigue.

T-cell proliferation is inhibited by daclizumab (anti-Tac; Zenapax®, Roche Pharmaceuticals, Basle, Switzerland), a humanized antibody that binds to the α-subunit (CD25) of the high-affinity IL-2 receptor (Tac).[104] The efficacy of daclizumab in patients with psoriasis is related to CD25 receptor blockade; activation of this receptor is critical for $CD4^+$ and $CD8^+$ T-cell activation and proliferation.[105] The CD25 receptor remained blocked when daclizumab was administered every 2 weeks; however, with less frequent dosing, variable desaturation of CD25 receptors began, and this reversal of effect was related to a slowing of disease improvement.[105] After the 8 weeks of treatment, patients with a baseline PASI < 36 responded with a mean improvement of 30% ($P = 0.02$). No significant adverse events or laboratory abnormalities were noted. It was suggested that daclizumab may be more effective in psoriasis when combined with another immunosuppressive agent, such as cyclosporin, to reduce circulating IL-2 production and decrease the likelihood of IL-2 competition with the antibody for CD25 binding.[105]

Immune deviation

Another approach for antipsoriatic therapies relies on a dual population of cytokine-secreting T cells: Th1 cells secrete proinflammatory cytokines (e.g. IFNγ, TNFα)[67] and the Th2 population secretes inhibitory cytokines (e.g. IL-4, IL-10).[106,107] Induction of immune deviation involves direct administration of a Th2 cytokine, such as IL-10, IL-11 or IL-4, to downregulate Th1 cells.[108–110] In early clinical trials, variable antipsoriatic efficacy has been observed with these agents. Further research is needed.

Cytokine inhibition

Agents that antagonize, bind or inactivate proinflammatory cytokines released by Th1 cells have a role in other inflammatory diseases and are being studied in psoriasis.[111] The two compounds with relevant clinical data are anti-TNFα agents.

Infliximab (Remicade®, Centocor, PA, USA), a humanized monoclonal antibody that binds with high affinity to soluble transmembrane forms of TNFα, is used in Crohn's disease but has also shown efficacy in psoriasis.[112] In a phase II study, 33 patients with moderate to severe plaque psoriasis were randomized to receive either placebo or infliximab 5 mg/kg or 10 mg/kg by 2-h IV infusion at weeks 0, 2 and 6.[113] The percentages of patients achieving a good, excellent or clear rating on PGA at week 10 were significantly higher in both infliximab groups (82% for 5 mg/kg and 91% for 10 mg/kg; $P < 0.01$) compared with placebo (18%). Similarly, 82% of patients receiving 5 mg/kg and 73% patients receiving 10 mg/kg had a ≥ 75% PASI reduction compared with 18% in the placebo group ($P < 0.01$ and $P = 0.03$, respectively).[113] Follow-up data through week 26 have been presented (American Academy of Dermatology, 2002) and showed that 55% and 48% of patients maintained a 50% or greater and a 75% or greater PASI reduction, respectively. No serious adverse events were reported, with headache more frequent in the infliximab 10-mg/kg group than in the placebo group. It should be considered, however, that clinical experience with infliximab in patients with rheumatoid arthritis or Crohn's disease has resulted in some cases of severe infection,[114–116] including tuberculosis, that may develop soon after initiation of anti-TNFα treatment.[117]

Etanercept (Enbrel®, Immunex, Seattle, WA, USA) is a fusion protein consisting of the extracellular domain of the human

TNFα receptor fused to the Fc portion of human IgG_1. The drug is currently approved for use in rheumatoid and psoriatic arthritis, but it has also demonstrated efficacy in recent clinical trials of psoriasis.[118] In a randomized, placebo-controlled, 12-week study, etanercept was administered at a dose of 25 mg twice weekly by SC injection to 60 patients. The median PASI improvement was 46% in etanercept-treated patients compared with 9% in placebo-treated patients ($P < 0.05$). Five (26%) etanercept-treated patients achieved a ≥ 75% PASI reduction after 12 weeks of treatment compared with none of the placebo patients ($P = 0.015$).[118] Improvement in psoriatic arthritis was also observed. Etanercept was well tolerated, with no serious adverse events reported. Patients treated with etanercept for rheumatoid arthritis have been reported to experience injection site reactions as well as serious infections in some cases.[119,120] Therefore, cautious use in patients with a history of recurring infections or with disease states that may predispose to infections is recommended.[119]

In a 24-week, multicentre, blinded, randomized study, 112 patients with psoriasis received either etanercept 25 mg or placebo. The percentage of patients achieving at least a 75% improvement in PASI at 12 weeks was significantly higher in the etanercept group compared with the placebo group (30% and 2%, respectively; $P < 0.0001$). Efficacy continued to improve over the next 12 weeks of treatment, with 54% of etanercept-treated patients and 5% of those receiving placebo achieving ≥ 75% PASI improvement at 24 weeks ($P < 0.0001$). Statistically significant improvements in patient global, physician global and target lesion assessments and DLQI also were observed following etanercept therapy. Etanercept was well tolerated, with similar incidences of adverse events between groups (70% for etanercept, 67% for placebo). (These data were presented at the Noah Worcester Dermatological Society, the Hawaii Dermatology Meeting, and the American Academy of Dermatology, 2002).

For both etanercept and infliximab, other adverse events encountered in clinical experience include formation of human antichimeric antibodies with associated acute and delayed hypersensitivity reactions, human-antihuman antibodies, and formation of autoantibodies with occasional instances of drug-induced lupus.[121,122] A recent report reviews temporary neurologic symptoms related to therapy with etanercept or infliximab that were partially or completely resolved on discontinuation in 19 patients.[123] It remains unknown whether long-term treatment of psoriasis with either of these agents will be associated with increased risk for any of these adverse events.

The anti-inflammatory activity of anti-IL-8 (ABX-IL-8, Abgenix, Fremount, CA, USA) is being evaluated in psoriasis.[124] This fully human, high-affinity monoclonal antibody blocks chemotaxis and proliferation by targeting IL-8 activity. Reduction in PASI has been observed in phase II trials following IV infusion of 3 mg/kg or 6 mg/kg every 3 weeks over a 12-week treatment period for a total of five doses. Patients were evaluated at Week 18, 6 weeks after the last dose. The biologic agent was well tolerated, with no serious drug-related or infusion-related adverse events. Additional trials are ongoing to further investigate the efficacy and safety of anti-IL-8 as well as the optimum dosing regimen.

Other immunomodulators

Two agents with atypical mechanisms of action recently reported to have antipsoriatic efficacy are the ascomycin macrolactam derivative, pimecrolimus (SDZ ASM 981; Elidel®, Novartis, Basel, Switzerland)[125] and a delipidated, deglycolipidated preparation of *Mycobacterium vaccae* (PVAC™, Genesis, NJ, USA).[126,127]

Pimecrolimus is being developed for the topical and oral treatment of dermatologic disorders.[125,128,129] Like its parent, ascomycin, and its immunomodulatory relatives tacrolimus (FK506) and sirolimus, this compound blocks calcineurin, inhibiting activation and cytoplasmic transport of nuclear factor of activated T cells (NF-ATp), and preventing T-cell transcription and release of proinflammatory Th1 cytokines (e.g. IL-12, IFNγ and TNFα) from T cells and mast cells.[129,130] Developed primarily for topical treatment of other skin diseases, pilot clinical trials are underway to evaluate its oral efficacy in chronic plaque psoriasis.[131]

Mycobacterium vaccae, a non-pathogenic organism administered intradermally as a heat-killed suspension, has been used as immunotherapy for tuberculosis and leprosy.[132] Its mechanism of action in psoriasis is unclear.[126,133] In an open pilot study of 20 patients with chronic plaque psoriasis, PVAC was given as two injections separated by 3 weeks.[127] After 12 weeks, 13 patients had > 50% reduction in PASI; three patients were unchanged, four had worsened with two of these developing exfoliative flares, leading to one withdrawal. Improvement in psoriasis was maintained in some responding patients at 4 weeks. Though these preliminary results are interesting, large-scale, randomized, double-blind, controlled trials are needed for both pimecrolimus and PVAC before their efficacy, safety and usefulness in the treatment of chronic plaque psoriasis can be fairly appraised.

Conclusions

A host of biologic agents are in development for psoriasis based on the central role of T cells in the pathogenesis of the disease. Because psoriasis is a chronic disease, the promise of these agents for improving outcomes is dependent on their safety and tolerability in long-term use, either chronically or intermittently. Agents with a remittive mechanism of action would offer additional benefits, providing patients with more time free of disease and off drug therapy. The use of biologic therapies will likely become a routine aspect of psoriasis management, much like other immune-mediated diseases.

As these treatments confirm the key role of T cells in psoriasis pathogenesis and pinpoint additional aspects of T-cell immunopathology, optimization of these therapies may become possible with identification of surrogate markers of disease. In addition, the use of biologic agents in combination with other biologic or traditional therapies for psoriasis may further improve overall response rates. Recognition of the antigenic trigger and/or genetic link for psoriasis also holds promise for future treatment options.

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